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Title: Title: Management and five year outcomes in 9978 women with screen detected DCIS: the UK Sloane Project.

Article Type: Original Research Article

Keywords: Ductal carcinoma in situ (DCIS); radiotherapy; margins; recurrence.

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Abstract: Background:

Management of screen-detected ductal carcinoma in situ (DCIS) remains controversial.

Methods:

A prospective cohort of DCIS diagnosed through the UK National Health Service Breast Screening Programme (1 April 2003 to 31 March 2012) was linked to national databases and case note review to analyse patterns of care, recurrence and mortality.

Results:

Screen-detected DCIS in 9938 women, mean age 60 years (range 46-87), was treated by mastectomy (2931) or breast conservation surgery (BCS) (7007; 70%). At 64 months median follow up, 697 (6.8%) had further DCIS or invasive breast cancer after BCS (7.8%) or mastectomy (4.5%) ($p < 0.001$). Breast radiotherapy (RT) after BCS (4363/7007; 62.3%) was associated with a 3.1% absolute reduction in ipsilateral recurrent DCIS or invasive breast cancer (No RT: 7.2% vs RT: 4.1% ($p < 0.001$) and a 1.9% absolute reduction for ipsilateral invasive breast recurrence (No RT: 3.8% vs RT: 1.9% ($p < 0.001$), independent of excision margin width or size of DCIS. Women without RT after BCS had more ipsilateral breast recurrences ($p < 0.001$) when the radial excision margin was < 2 mm. Adjuvant endocrine therapy (1208/9938; 12%) was associated with a reduction in any ipsilateral recurrence, whether RT was received (HR 0.57: 95% CI 0.41 - 0.80) or not (HR 0.68: 95% CI 0.51 - 0.91) after BCS. Women who developed invasive breast recurrence had a worse survival than those with recurrent DCIS ($p < 0.001$). Among 321 (3.2%) who died, only 46 deaths were attributed to invasive breast cancer.

Conclusion:

Recurrent DCIS or invasive cancer is uncommon following screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. Further research to identify biomarkers of recurrence risk, particularly as invasive disease, is indicated.

Ms. Ref. No.: EJC-D-18-00766
European Journal Of Cancer

Many thanks for your further editorial suggestions. I have included these in the uploaded revision notes with a point by point response.

The title has been changed and shortened as requested

- please shorten the highlights before or after the study a.o. by using telegram style

Done

- make the titles of tables and figures more informative (time and place) so that they could also be used more easily for presentations

This has been done although we struggled to include time and place in the titles

- for historical reasons it would be interesting to indicate in time when the DCIS problem became a relevant problem (40-50 years ago?) (I remember that this was already mentioned by pathologists in Holland in 1979 as a serious problem (born around 1905) and hopes for adequate biomarkers were uttered

Some time literature searching identified some publications in the 30s and 40s! – The earliest of these has been referenced

The work of Nederend et al. upon introduction of digital mammography make clear that it needs to become worse before becoming better (hopefully)

I mentioned earlier that Hazel Thornton has made a huge problem of this in the 1990's . I would appreciate if you referred to her work as well

This has been done. It seemed best suited to the discussion [ref 26]

With best regards

D Dodwell

European Journal of Cancer

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(Please ensure that a 'Conflict of Interest' statement is included in your manuscript)

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"I confirm that all the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to the *European Journal of Cancer*".

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Ms. Ref. No.: EJC-D-18-00766

**Title: A prospective, national cohort study of treatment and outcomes for screen-detected ductal carcinoma in situ (DCIS) of the breast.
European Journal Of Cancer**

Responses to Editor comments:

thank you for extensive revisions. (my apology for delay)

I only have a few requests related to readability

- a (more) challenging title (current one is rather boring); also with an indication of calendar time and country (instead of national)

The title has been changed and shortened as requested

- please shorten the highlights before or after the study a.o. by using telegram style

Done

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This has been done. It seemed best suited to the discussion [ref 26]

Evidence before this study - Highlights

- DCIS represents 20-25% of screen-detected breast cancer.
- Management remains controversial .
- Adjuvant radiotherapy (RT) following wide excision reduces ipsilateral recurrence but not mortality
- A 2mm surgical excision margin is widely recommended
- Survival following treatment of DCIS is excellent, with few subsequent deaths from breast cancer.

Added value of this study

- Further DCIS or invasive breast cancer is not uncommon (6.8% at 5 years)
- Breast RT was associated with reductions in ipsilateral breast events independent of width of margin of excision or size of DCIS.
- Endocrine therapy was rarely utilised.
- 5 year mortality was not impacted by use of radiotherapy or endocrine therapy.

Title: Management and five year outcomes in 9978 women with screen detected DCIS: the UK Sloane Project~~A prospective, national cohort study of treatment and outcomes for screen-detected ductal carcinoma in situ (DCIS) of the breast.~~

Authors: Alastair M Thompson ^a, Karen Clements ^b, Shan Cheung ^b, Sarah E Pinder ^c, Gill Lawrence ^b, Elinor Sawyer ^c, Olive Kearins ^b, Graham R Ball ^d, Ian Tomlinson ^e, Andrew Hanby ^f, Jeremy St J Thomas ^g, Anthony J Maxwell ^h, Matthew G Wallis ⁱ, David J Dodwell ^j. On behalf of the Sloane Project Steering Group (NHS Prospective Study of Screen-Detected Non-invasive Neoplasias).

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Abstract

Background:

Management of screen-detected ductal carcinoma *in situ* (DCIS) remains controversial.

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A prospective cohort of DCIS diagnosed through the UK National Health Service Breast Screening Programme (1 April 2003 to 31 March 2012) was linked to national databases and case note review to analyse patterns of care, recurrence and mortality.

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Screen-detected DCIS in 9938 women, mean age 60 years (range 46-87), was treated by mastectomy (2931) or breast conservation surgery (BCS) (7007; 70%). At 64 months median follow up, 697 (6.8%) had further DCIS or invasive breast cancer after BCS (7.8%) or mastectomy (4.5%) ($p < 0.001$). Breast radiotherapy (RT) after BCS (4363/7007; 62.3%) was associated with a 3.1% absolute reduction in ipsilateral recurrent DCIS or invasive breast cancer (No RT: 7.2% vs RT: 4.1% ($p < 0.001$)) and a 1.9% absolute reduction for ipsilateral invasive breast recurrence (No RT: 3.8% vs RT: 1.9% ($p < 0.001$)), independent of excision margin width or size of DCIS. Women without RT after BCS had more ipsilateral breast recurrences ($p < 0.001$) when the radial excision margin was < 2 mm. Adjuvant endocrine therapy (1208/9938; 12%) was associated with a reduction in any ipsilateral recurrence, whether RT was received (HR 0.57: 95% CI 0.41 - 0.80) or not (HR 0.68: 95% CI 0.51 - 0.91) after BCS. Women who developed invasive breast recurrence had a worse survival than those with recurrent DCIS ($p < 0.001$). Among 321 (3.2%) who died, only 46 deaths were attributed to invasive breast cancer.

Conclusion:

Recurrent DCIS or invasive cancer is uncommon following screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. Further research to identify biomarkers of recurrence risk, particularly as invasive disease, is indicated.

Keywords: Ductal carcinoma in situ (DCIS); radiotherapy; margins; recurrence.

Introduction

Ductal carcinoma *in situ* (DCIS) comprises 20-25% of screen-detected breast cancer and, like invasive breast cancer, is heterogeneous in terms of underlying biology, presentation and outcome [1]. The clinical behaviour of DCIS is unpredictable, challenging clinical decision-making. Recently, concern regarding the over-treatment of DCIS [1], has been fueled by large retrospective American series demonstrating excellent (>95%) long term survival 10-20 years after diagnosis although others have suggested that detection and treatment of screen-detected DCIS may prevent subsequent invasive disease. [2-4]

Standard treatment for DCIS includes mastectomy or breast conserving surgery (BCS), with or without radiotherapy (RT) and/or endocrine therapy to decrease ipsilateral recurrence and/or contralateral breast carcinoma. [5-7] It remains unclear which patients benefit from these adjuvant therapies. Prospective data are lacking and the clinical significance of early detection and treatment for DCIS remains unclear. Here, we report the first analysis of recurrence and mortality from a prospective cohort study of DCIS detected through a contemporary national screening programme. Utilising diagnostic imaging, surgery, histopathology and adjuvant therapy data provided by the local breast screening unit where diagnosis was reached, along with longitudinal follow-up of patients through case note review and linkage to national databases, we describe the features and outcomes following diagnosis of screen-detected DCIS.

Methods

The United Kingdom National Health Service Breast Screening Programme (NHSBSP) invites women aged 50-70 to attend breast screening every three years (*supplementary figure and text p2*). The Sloane Project was established in memory of Professor John Sloane, a breast pathologist, to audit the features, patterns of care and outcomes for women with non-invasive neoplasia detected within the NHSBSP. Data capture was via radiology, pathology, surgery and radiotherapy (RT) paper proformas collected at screening unit level, sent to Public Health England, then each patient's data entered on a secure database held on an SQL server that generated an individual patient and tumour identifier. The data reported here is for women in the dataset who had DCIS

identified. For the 34 women with bilateral DCIS, the higher grade and/or larger lesion was considered the index.

Data included demographic, diagnostic, treatment and vital status. Adherence to NHSBSP guidelines and participation in the relevant quality assurance programmes were mandatory. Participating units were required to follow a pathology protocol containing definitions for DCIS, microinvasion, cytonuclear grade, comedo necrosis and assessment of excision margins and to handle and report specimens to NHSBSP pathology standards. [8] Radiology guidelines mandated participating radiologists should complete detailed radiology proformas [9] and participate in the NHSBSP PERFORMS external quality assurance scheme. [10]

Missing (unknown) data were rare for key comparisons including use of radiotherapy (0.5%), grade of DCIS (0.1%), lesion size (0.4%) or cause of death (0.1%). Events were identified by matching women by NHS number and date of birth to information provided by breast screening units, and to routinely collected UK datasets including Hospital Episode Statistics (HES), Cancer Waiting Times (CWT), the English Cancer Analysis System (CAS)/National Cancer Registration and Analysis Service (NCRAS), the English National Radiotherapy Dataset (RTDS) and the Information Services Division, Scotland (ISD). The census date was the date of death or 31 December 2012. Validation of data was undertaken by cross-checking with original screening unit source documents for those patients with recurrence and more generally, for the overall dataset, against the Association of Breast Surgery national audits 2006-2012.

Ethics Committee approval was not required for this prospective cohort study originally conducted under the NHS Cancer Screening Programme's application to the Patient Information Advisory Group (PIAG). More recently, access to patient data was approved to quality assure National Cancer Screening Programmes under the Health and Social Care Act 2006 (Section 251) via the Confidentiality Advisory Group (CAG).

Classification of recurrence & mortality

Given the difficulties in distinguishing local recurrence versus a new primary lesion in the same breast, the following terminology was used (*see supplementary figure and text p 2-3*). A 'breast event' was defined as (any of): ipsilateral breast recurrence (or new primary) after BCS; ipsilateral

recurrence (includes post-mastectomy/chest wall recurrence); regional or distant recurrence; or contralateral re/occurrence. (See supplementary figure and text, [p3-4] for definitions of mortality).

Statistical analyses

Logistic linear regression analysis was used to test the relationship between a binary variable and continuous or ordered categorical dependent variables. The importance of factors was determined by likelihood ratio tests that compared the full model and a reduced model with one factor removed at a time. A factor with a lower p-value from the likelihood ratio test was deemed to be more important than one with a higher p-value.

For disease recurrence, cumulative incidence plots were produced, taking account of the competing risks between recurrence and death. K-sample tests were performed to compare the groups in the cumulative incidence plots. For overall and breast cancer specific survival, Kaplan-Meier survival plots were produced; log rank tests were used to test the difference between survival curves. All time to event analyses were performed using the Cox semi-parametric proportional hazard regression. Tied times were adjusted using the Breslow's method. The proportional hazard assumption was assessed by Schoenfeld residuals test. For most analyses, the proportional hazard assumption is valid. Analyses were performed in R. Considering the high number of variables and groups within the variables, probability values lower than one in a hundred (0.01) were used to assign statistical significance.

Results

Patterns of care

From 12,788 patients (12,838 non-invasive lesions) diagnosed from 1 April 2003 to 31 March 2012 complete data were available for 9938 women (age range 46-87, mean age 60) diagnosed with DCIS (with or without lobular carcinoma in situ (LCIS) and/or atypical ductal hyperplasia (ADH)) (Figure 1). Seventy-eight breast screening units in England and Scotland contributed data (82% of the 95 units). Median follow up was 64 months (range 6 - 116 months). Over the same decade in the UK, 30,187 women were diagnosed with non-invasive and microinvasive breast cancers through the NHSBSP; thus, the data analysed represent 77% (9938/12,838) of non-invasive lesions

within this prospective cohort, and 33% (9938/30,187) of women with a final diagnosis of in situ breast carcinoma diagnosed through the NHSBSP.

Surgical treatment

Breast conservation surgery (BCS) was definitive surgery in 7007 (70%) women and was utilised more often with increasing age up to 59 years and thereafter appeared constant. Mastectomy was definitive surgery for 2931 (30%) women. The use of mastectomy was associated with DCIS of high or intermediate rather than low grade ($p<0.001$) and with larger lesion size ($p<0.001$). The use of BCS versus mastectomy was unchanged over time.

Radiotherapy

For 7007 women who had BCS, 62% also had RT; the use of RT increased over time ($p<0.001$). Women aged 70 or older were less likely to have RT compared to women aged 50-70 ($p=0.006$). Use of RT after BCS increased with grade of DCIS ($p<0.001$), DCIS size ($p<0.001$), the presence of microinvasion ($p<0.001$) and comedo necrosis ($p<0.001$), but not with margin width (Table 1), confirmed by multivariable analysis (result not shown). RT was administered after mastectomy in 33 (1%) women, as previously reported. [11]

Endocrine Therapy

Endocrine therapy was prescribed to more women following BCS (14%) than mastectomy (8%) ($p<0.001$). The use of endocrine therapy was not related to age and was prescribed less frequently over time ($p<0.001$). There was no relationship between the receipt of endocrine therapy and RT use after BCS.

Outcomes

At a median follow up of 64 months, 6.8% of women (679/9938) had a breast (DCIS or invasive) event: 451 (4.5%) were ipsilateral breast, regional or distant recurrences and 228 (2.3%) represented a re/occurrence in the contralateral breast/nodes. Ipsilateral breast recurrence after BCS was 5.3% (368/7007); ipsilateral chest wall recurrence after mastectomy was 0.8% (24/2931). The risk of a further breast event did not differ by year of screening.

Recurrence following BCS

Following BCS, there was a greater risk of ipsilateral breast recurrence for those who did not have RT compared to those who had RT ($p<0.001$, HR=0.59: 95% CI 0.53 - 0.67) (no RT: 7.2% vs RT: 4.1%) (Figure 2). There was a significantly lower risk of invasive ipsilateral breast recurrence (no RT: 3.8% vs RT: 1.9%) ($p<0.001$, HR=0.51: 95% CI 0.43 - 0.60) but not ipsilateral DCIS recurrence (no RT: 3.3% vs RT: 2.2%) ($p=0.05$, HR=0.69: 95% CI =0.58 - 0.82.) in women who received RT.

After BCS, the risk of developing ipsilateral breast recurrence was greater in patients with a negative or close DCIS margin (0 to <2mm: 7.4% vs ≥ 2 mm: 4.8%; $p<0.001$, HR=0.67: 95% CI 0.57 - 0.78), ($p<0.001$) whether patients received RT ($p=0.011$, HR=0.75: 95% CI 0.60 - 0.94) or not ($p<0.001$, HR=0.59: 95% CI 0.47 - 0.73).

RT and endocrine therapy were independently associated with a decreased risk of ipsilateral breast recurrence (RT: $p<0.001$, HR=0.59: 95% CI 0.52 – 0.66; endocrine therapy; $p=0.003$, HR=0.7: 95% CI 0.55 – 0.89; interaction: $p=0.20$).

Multivariable analyses for recurrence

By multivariable analyses, following BCS, use of RT (HR 0.38: 95% CI 0.33-0.45) and endocrine therapy (HR 0.63: 95% CI 0.50 - 0.78) were each independently associated with a significantly reduced risk of breast events and ipsilateral breast recurrence (RT: HR 0.40: 95% CI 0.34 - 0.48) (endocrine therapy: HR 0.56: 95% CI 0.44 - 0.72).

After adjusting for all other factors, the presence of high grade of DCIS and of comedo necrosis were significantly associated with a higher risk of breast events (excluding contralateral occurrence) (high grade - HR 1.50: 95% CI 1.14 - 1.98, comedo necrosis HR 1.31: 95% CI 1.09 - 1.57) and of ipsilateral breast recurrence (high grade - HR 1.40: 95% CI 1.05 - 1.87); comedo necrosis - HR 1.30: (95% CI 1.07 – 1.57).

Contralateral disease

Contralateral breast cancer was seen in 218 women (2.2%); more commonly after mastectomy (81/2931; 2.8%) than after BCS (137/7007; 1.9%) ($p < 0.001$).

Survival

Among the 9938 women, there were 321 deaths (3.2%), 46 attributed to breast cancer. There was no difference in overall (or breast cancer-related) mortality comparing BCS (3.1% [218/7007]) to mastectomy (3.5% [103/2931]).

Women treated with RT after BCS had a lower all-cause mortality (RT: 2.5% vs no RT: 4.2%; $p < 0.001$), even when corrected for age ($p < 0.001$, HR=0.65: 95% CI 0.49 - 0.85), but not a lower breast cancer mortality ($p = 0.41$, HR=0.73: 95% CI 0.34 - 1.56). The use of endocrine therapy was not associated with overall or breast cancer specific mortality.

Women who developed an invasive breast recurrence had a significantly worse overall survival (log rank p -value < 0.001) and breast cancer specific survival (log rank p -value < 0.001) from the time of the further event compared with those who developed recurrent DCIS (Figure 3) (*supplementary figure 1*).

Discussion

This study of 9938 women with DCIS detected through the UK NHSBSP confirms that recurrent DCIS or invasive cancer remains a concern following modern management of screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. The present prospective cohort study contrasts with recent but retrospective studies of US [2, 3] and European data. [12] Unlike those series, we report prospectively collected data from the setting of an established national breast screening programme, with built in quality assurance of imaging, surgery, pathology and RT. [10, 13] An additional major strength, in contrast to other studies including the randomised clinical trials, is the prospective collection of margin status, an area of significant international controversy. In addition, available data include the use of endocrine therapy with linkage to outcomes. [2, 3] Conversely, one limitation of the present study, in keeping with the recently published retrospective series [2-4, 12] is its observational nature with the consequent difficulty in

accounting for all possible confounders. Follow up is also relatively short in the context of the long natural history of DCIS.

Breast conservation was the definitive surgery for 70.5% of women, more frequently used with increasing age. This may reflect perceptions about risk of within breast recurrence in younger patients. Whilst it is likely that RT following BCS was used in patients perceived (based on pathological and patient-related factors) to be at higher risk of recurrence, RT use was, surprisingly, not associated with close or involved circumferential resection margins. Conversely, mastectomy was, not unexpectedly, associated with features of more aggressive DCIS.

RT following BCS was associated with a significant reduction in all ipsilateral breast further events (DCIS or invasive) at a median follow up of 64 months. The association of RT with reduced recurrence risk is consistent with the effects seen in the overview of the prospective randomized trials. [14] Significantly, however, in the present study, the reduction of breast recurrence associated with RT was independent of margin of excision. Differing minimum margin widths for DCIS have been proposed [15, 16]. One recent series has suggested that a 1mm margin may be sufficient, with or without RT [17]. Others have suggested that those with margin widths <1mm may benefit from postoperative radiation therapy whilst those with >10mm margins receive no benefit with regard to recurrence. [18] However, specifically for women who did not receive RT, in this series there was an association between a DCIS margin of <2mm and ipsilateral breast recurrence. This provides direct evidence in support of more recent reviews, meta-analysis and consensus guidelines [19, 20] as well as recent studies [21].

The higher all-cause mortality in patients not receiving RT after BCS is likely to reflect comorbidities not captured in the current study. Nevertheless, patients not receiving RT had a higher (7.2%) breast recurrence rate, confirming patient selection for RT could be improved. [22] Endocrine therapy was associated with a non-significant reduction in ipsilateral breast recurrence independent of RT, although the greatest effect was seen for the reduction of invasive further events in the absence of RT. In a contemporary analysis of the US retrospective National Cancer Data Base (70% of the US population), 36.5% of women (most commonly between 50 and 59 years of age) received adjuvant endocrine therapy for DCIS [23] compared with 12.2% in this UK-based study, and no-one in a cohort in the Netherlands [12], reflecting the inconsistent interpretation of

evidence from trials examining the impact of endocrine therapy for DCIS on local recurrence, the associated toxicities and issues of adherence to adjuvant tamoxifen treatment.

Significantly, neither the use of RT, endocrine therapy, nor type of surgery, appeared to influence breast cancer mortality, although women who developed invasive ipsilateral breast cancer had a poorer survival than those who had DCIS recurrence. Indeed, breast cancer mortality (0.46%) was a fifth of other cause mortality, in keeping with several retrospective studies. [2, 3, 12]

The increasing incidence of DCIS, likely to be sustained with the enhanced visualisation that digital mammography provides, now deployed in the UK NHS BSP, emphasises the potential for overtreatment of women diagnosed through breast screening. [1] Since digital mammography was not deployed during the time of data collection for this study, the impact of digital mammography and any influences on the data reported here remain uncertain. However, the present study findings do re-emphasise the issue of potential overtreatment of DCIS and the need to improve the selection of adjuvant therapy for women with DCIS. This requires a greater understanding of the underlying biology of DCIS, on reliable predictive and prognostic assessment, particularly to select women at risk of invasive breast cancer recurrence. Predictive models of ipsilateral breast recurrence after DCIS, and a more recent prognostic score for DCIS for RT benefit, require prospective validation if they are to be widely adopted. [24-28] Meanwhile, a major international initiative between the UK, Netherlands and the US, the PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) study funded by Cancer Research UK and the Dutch Cancer Society seeks to define underlying molecular mechanisms in DCIS related to risk of progression and, together with diagnostic and clinical elements, construct risk models for the future management of patients. (<http://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award/funded-teams-wesseling>) [28] Emulating studies in prostate, thyroid and renal neoplasia, active surveillance, rather than initial surgery, for carefully selected patients with low risk DCIS has been advocated and may avoid the potential sequelae of breast surgery. Indeed, prospective randomised trials of active surveillance versus conventional surgical care, e.g. the LOW RISK DCIS (LORIS) trial in the UK, COMET in the USA and LORD in mainland Europe [29-31] seek to identify a cohort of patients with sufficiently low risk to obviate the need for surgical excision.

Conclusions

This large prospective cohort study allows us to examine, in contemporary practice, the effects of present-day treatments, and the patient and pathological features that have previously been described in retrospective studies and randomised clinical trials. The reduction in recurrence rates seen with the use of RT and endocrine therapy has not, to date, yielded a survival benefit to patients, although other-cause mortality is five times greater than that attributable to breast cancer. Ipsilateral breast recurrence risk is, however, higher in patients treated by BCS without RT, particularly if the radial excision margin is narrow (<2mm). Women with recurrence as invasive disease have poorer survival than those with recurrent DCIS and further research targeting clinical, biological and imaging biomarkers of risk of invasive recurrence after a diagnosis of screen-detected DCIS is indicated, to improve personalisation of therapy and outcomes.

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Appendix

UK Breast Screening Units contributing to the Sloane Project:

Avon	North Derbyshire
Barking, Havering, Redbridge & Brentwood	North East Scotland
Barnsley	North Lancashire & South Cumbria
Bedfordshire & Hertfordshire	North London
Bolton, Bury & Rochdale	North Nottinghamshire
Breast Test Wales – North*	North Staffordshire
Breast Test Wales – South East*	North Yorkshire
Breast Test Wales – South West*	Northampton
Cambridge & Huntingdon	Nottingham
Central & East London	Oxfordshire
Chelmsford & Colchester	Pennine (Bradford)
Chester	Peterborough
City, Sandwell & Walsall	Portsmouth
Cornwall	Rotherham
Crewe	Sheffield
Doncaster	Shropshire
Dorset	Somerset
Dudley & Wolverhampton	South Birmingham
East Berkshire (Windsor)	South Derbyshire
East Cheshire & Stockport	South Devon
East Lancashire	South East London & Queen Mary's
East Scotland	South East Scotland
East Sussex, Brighton & Hove	South Essex
Gateshead	South Staffordshire
Gloucestershire	South West London (St George's)
Great Yarmouth & Waveney	South West Scotland
Greater Manchester	Southampton & Salisbury
Hereford & Worcester	Surrey (Jarvis)
Humberside	Warrington

Isle of Wight	Warwickshire, Solihull & Coventry
King's Lynn	West Berkshire
Leeds & Wakefield	West Devon & East Cornwall
Leicestershire	West Essex
Liverpool	West of London
Maidstone	West of Scotland
Medway (Gillingham, Kent)	West Suffolk
Milton Keynes	Western, Northern Ireland*
Newcastle-Upon-Tyne	Wiltshire
Norfolk & Norwich	Wirral
North & Eastern Devon	Wycombe
North & Mid Hampshire	
North Cumbria	

* Unit data not included in these analyses

Title: Management and five year outcomes in 9978 women with screen detected DCIS: the UK Sloane Project.

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Abstract

Background:

Management of screen-detected ductal carcinoma *in situ* (DCIS) remains controversial.

Methods:

A prospective cohort of DCIS diagnosed through the UK National Health Service Breast Screening Programme (1 April 2003 to 31 March 2012) was linked to national databases and case note review to analyse patterns of care, recurrence and mortality.

Results:

Screen-detected DCIS in 9938 women, mean age 60 years (range 46-87), was treated by mastectomy (2931) or breast conservation surgery (BCS) (7007; 70%). At 64 months median follow up, 697 (6.8%) had further DCIS or invasive breast cancer after BCS (7.8%) or mastectomy (4.5%) ($p < 0.001$). Breast radiotherapy (RT) after BCS (4363/7007; 62.3%) was associated with a 3.1% absolute reduction in ipsilateral recurrent DCIS or invasive breast cancer (No RT: 7.2% vs RT: 4.1% ($p < 0.001$)) and a 1.9% absolute reduction for ipsilateral invasive breast recurrence (No RT: 3.8% vs RT: 1.9% ($p < 0.001$)), independent of excision margin width or size of DCIS. Women without RT after BCS had more ipsilateral breast recurrences ($p < 0.001$) when the radial excision margin was < 2 mm. Adjuvant endocrine therapy (1208/9938; 12%) was associated with a reduction in any ipsilateral recurrence, whether RT was received (HR 0.57: 95% CI 0.41 - 0.80) or not (HR 0.68: 95% CI 0.51 - 0.91) after BCS. Women who developed invasive breast recurrence had a worse survival than those with recurrent DCIS ($p < 0.001$). Among 321 (3.2%) who died, only 46 deaths were attributed to invasive breast cancer.

Conclusion:

Recurrent DCIS or invasive cancer is uncommon following screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. Further research to identify biomarkers of recurrence risk, particularly as invasive disease, is indicated.

Keywords: Ductal carcinoma in situ (DCIS); radiotherapy; margins; recurrence.

Introduction

Although described over 80 years ago [1] ductal carcinoma *in situ* (DCIS) became a common management problem after the introduction of breast screening and now comprises 20-25% of screen-detected breast cancer. Like invasive breast cancer, DCIS is heterogeneous in terms of underlying biology, presentation and outcome [2]. The clinical behaviour of DCIS is unpredictable, challenging clinical decision-making. Recently, concern regarding the over-treatment of DCIS [2], has been fueled by large retrospective American series demonstrating excellent (>95%) long term survival 10-20 years after diagnosis although others have suggested that detection and treatment of screen-detected DCIS may prevent subsequent invasive disease. [3-5]

Standard treatment for DCIS includes mastectomy or breast conserving surgery (BCS), with or without radiotherapy (RT) and/or endocrine therapy to decrease ipsilateral recurrence and/or contralateral breast carcinoma. [6-8] It remains unclear which patients benefit from these adjuvant therapies. Prospective data are lacking and the clinical significance of early detection and treatment for DCIS remains unclear. Here, we report the first analysis of recurrence and mortality from a prospective cohort study of DCIS detected through a contemporary national screening programme. Utilising diagnostic imaging, surgery, histopathology and adjuvant therapy data provided by the local breast screening unit where diagnosis was reached, along with longitudinal follow-up of patients through case note review and linkage to national databases, we describe the features and outcomes following diagnosis of screen-detected DCIS.

Methods

The United Kingdom National Health Service Breast Screening Programme (NHSBSP) invites women aged 50-70 to attend breast screening every three years (*supplementary figure and text p2*). The Sloane Project was established in memory of Professor John Sloane, a breast pathologist, to audit the features, patterns of care and outcomes for women with non-invasive neoplasia detected within the NHSBSP. Data capture was via radiology, pathology, surgery and radiotherapy (RT) paper proformas collected at screening unit level, sent to Public Health England, then each patient's data entered on a secure database held on an SQL server that generated an individual patient and tumour identifier.

The data reported here is for women in the dataset who had DCIS identified. For the 34 women with bilateral DCIS, the higher grade and/or larger lesion was considered the index.

Data included demographic, diagnostic, treatment and vital status. Adherence to NHSBSP guidelines and participation in the relevant quality assurance programmes were mandatory. Participating units were required to follow a pathology protocol containing definitions for DCIS, microinvasion, cytonuclear grade, comedo necrosis and assessment of excision margins and to handle and report specimens to NHSBSP pathology standards. [9] Radiology guidelines mandated participating radiologists should complete detailed radiology proformas [10] and participate in the NHSBSP PERFORMS external quality assurance scheme. [11]

Missing (unknown) data were rare for key comparisons including use of radiotherapy (0.5%), grade of DCIS (0.1%), lesion size (0.4%) or cause of death (0.1%). Events were identified by matching women by NHS number and date of birth to information provided by breast screening units, and to routinely collected UK datasets including Hospital Episode Statistics (HES), Cancer Waiting Times (CWT), the English Cancer Analysis System (CAS)/National Cancer Registration and Analysis Service (NCRAS), the English National Radiotherapy Dataset (RTDS) and the Information Services Division, Scotland (ISD). The census date was the date of death or 31 December 2012. Validation of data was undertaken by cross-checking with original screening unit source documents for those patients with recurrence and more generally, for the overall dataset, against the Association of Breast Surgery national audits 2006-2012.

Ethics Committee approval was not required for this prospective cohort study originally conducted under the NHS Cancer Screening Programme's application to the Patient Information Advisory Group (PIAG). More recently, access to patient data was approved to quality assure National Cancer Screening Programmes under the Health and Social Care Act 2006 (Section 251) via the Confidentiality Advisory Group (CAG).

Classification of recurrence & mortality

Given the difficulties in distinguishing local recurrence versus a new primary lesion in the same breast, the following terminology was used (*see supplementary figure and text p 2-3*). A 'breast event' was defined as (any of): ipsilateral breast recurrence (or new primary) after BCS; ipsilateral

recurrence (includes post-mastectomy/chest wall recurrence); regional or distant recurrence; or contralateral re/occurrence. (See supplementary figure and text, [p3-4] for definitions of mortality).

Statistical analyses

Logistic linear regression analysis was used to test the relationship between a binary variable and continuous or ordered categorical dependent variables. The importance of factors was determined by likelihood ratio tests that compared the full model and a reduced model with one factor removed at a time. A factor with a lower p-value from the likelihood ratio test was deemed to be more important than one with a higher p-value.

For disease recurrence, cumulative incidence plots were produced, taking account of the competing risks between recurrence and death. K-sample tests were performed to compare the groups in the cumulative incidence plots. For overall and breast cancer specific survival, Kaplan-Meier survival plots were produced; log rank tests were used to test the difference between survival curves. All time to event analyses were performed using the Cox semi-parametric proportional hazard regression. Tied times were adjusted using the Breslow's method. The proportional hazard assumption was assessed by Schoenfeld residuals test. For most analyses, the proportional hazard assumption is valid. Analyses were performed in R. Considering the high number of variables and groups within the variables, probability values lower than one in a hundred (0.01) were used to assign statistical significance.

Results

Patterns of care

From 12,788 patients (12,838 non-invasive lesions) diagnosed from 1 April 2003 to 31 March 2012 complete data were available for 9938 women (age range 46-87, mean age 60) diagnosed with DCIS (with or without lobular carcinoma in situ (LCIS) and/or atypical ductal hyperplasia (ADH)) (Figure 1). Seventy-eight breast screening units in England and Scotland contributed data (82% of the 95 units). Median follow up was 64 months (range 6 - 116 months). Over the same decade in the UK, 30,187 women were diagnosed with non-invasive and microinvasive breast cancers through the NHSBSP; thus, the data analysed represent 77% (9938/12,838) of non-invasive lesions within this prospective cohort, and 33% (9938/30,187) of women with a final diagnosis of in situ breast carcinoma diagnosed through the NHSBSP.

Surgical treatment

Breast conservation surgery (BCS) was definitive surgery in 7007 (70%) women and was utilised more often with increasing age up to 59 years and thereafter appeared constant. Mastectomy was definitive surgery for 2931 (30%) women. The use of mastectomy was associated with DCIS of high or intermediate rather than low grade ($p<0.001$) and with larger lesion size ($p<0.001$). The use of BCS versus mastectomy was unchanged over time.

Radiotherapy

For 7007 women who had BCS, 62% also had RT; the use of RT increased over time ($p<0.001$). Women aged 70 or older were less likely to have RT compared to women aged 50-70 ($p=0.006$). Use of RT after BCS increased with grade of DCIS ($p<0.001$), DCIS size ($p<0.001$), the presence of microinvasion ($p<0.001$) and comedo necrosis ($p<0.001$), but not with margin width (Table 1), confirmed by multivariable analysis (result not shown). RT was administered after mastectomy in 33 (1%) women, as previously reported. [12]

Endocrine Therapy

Endocrine therapy was prescribed to more women following BCS (14%) than mastectomy (8%) ($p<0.001$). The use of endocrine therapy was not related to age and was prescribed less frequently over time ($p<0.001$). There was no relationship between the receipt of endocrine therapy and RT use after BCS.

Outcomes

At a median follow up of 64 months, 6.8% of women (679/9938) had a breast (DCIS or invasive) event: 451 (4.5%) were ipsilateral breast, regional or distant recurrences and 228 (2.3%) represented a re/occurrence in the contralateral breast/nodes. Ipsilateral breast recurrence after BCS was 5.3% (368/7007); ipsilateral chest wall recurrence after mastectomy was 0.8% (24/2931). The risk of a further breast event did not differ by year of screening.

Recurrence following BCS

Following BCS, there was a greater risk of ipsilateral breast recurrence for those who did not have RT compared to those who had RT ($p<0.001$, HR=0.59: 95% CI 0.53 - 0.67) (no RT: 7.2% vs RT: 4.1%) (Figure 2). There was a significantly lower risk of invasive ipsilateral breast recurrence (no RT: 3.8% vs RT: 1.9%) ($p<0.001$, HR=0.51: 95% CI 0.43 - 0.60) but not ipsilateral DCIS recurrence (no RT: 3.3% vs RT: 2.2%) ($p=0.05$, HR=0.69: 95% CI =0.58 - 0.82.) in women who received RT.

After BCS, the risk of developing ipsilateral breast recurrence was greater in patients with a negative or close DCIS margin (0 to <2mm: 7.4% vs ≥ 2 mm: 4.8%; $p<0.001$, HR=0.67: 95% CI 0.57 - 0.78), ($p<0.001$) whether patients received RT ($p=0.011$, HR=0.75: 95% CI 0.60 - 0.94) or not ($p<0.001$, HR=0.59: 95% CI 0.47 - 0.73).

RT and endocrine therapy were independently associated with a decreased risk of ipsilateral breast recurrence (RT: $p<0.001$, HR=0.59: 95% CI 0.52 – 0.66; endocrine therapy; $p=0.003$, HR=0.7: 95% CI 0.55 – 0.89; interaction: $p=0.20$).

Multivariable analyses for recurrence

By multivariable analyses, following BCS, use of RT (HR 0.38: 95% CI 0.33-0.45) and endocrine therapy (HR 0.63: 95% CI 0.50 - 0.78) were each independently associated with a significantly reduced risk of breast events and ipsilateral breast recurrence (RT: HR 0.40: 95% CI 0.34 - 0.48) (endocrine therapy: HR 0.56: 95% CI 0.44 - 0.72).

After adjusting for all other factors, the presence of high grade of DCIS and of comedo necrosis were significantly associated with a higher risk of breast events (excluding contralateral occurrence) (high grade - HR 1.50: 95% CI 1.14 - 1.98, comedo necrosis HR 1.31: 95% CI 1.09 - 1.57) and of ipsilateral breast recurrence (high grade - HR 1.40: 95% CI 1.05 - 1.87); comedo necrosis - HR 1.30: (95% CI 1.07 – 1.57).

Contralateral disease

Contralateral breast cancer was seen in 218 women (2.2%); more commonly after mastectomy (81/2931; 2.8%) than after BCS (137/7007; 1.9%) ($p<0.001$).

Survival

Among the 9938 women, there were 321 deaths (3.2%), 46 attributed to breast cancer. There was no difference in overall (or breast cancer-related) mortality comparing BCS (3.1% [218/7007]) to mastectomy (3.5% [103/2931]).

Women treated with RT after BCS had a lower all-cause mortality (RT: 2.5% vs no RT: 4.2%; $p < 0.001$), even when corrected for age ($p < 0.001$, HR=0.65: 95% CI 0.49 - 0.85), but not a lower breast cancer mortality ($p = 0.41$, HR=0.73: 95% CI 0.34 - 1.56). The use of endocrine therapy was not associated with overall or breast cancer specific mortality.

Women who developed an invasive breast recurrence had a significantly worse overall survival (log rank p -value < 0.001) and breast cancer specific survival (log rank p -value < 0.001) from the time of the further event compared with those who developed recurrent DCIS (Figure 3) (*supplementary figure 1*).

Discussion

This study of 9938 women with DCIS detected through the UK NHSBSP confirms that recurrent DCIS or invasive cancer remains a concern following modern management of screen-detected DCIS. Both RT and endocrine therapy were associated with a reduction in further events but not with breast cancer mortality within 5 years of diagnosis. The present prospective cohort study contrasts with recent but retrospective studies of US [3, 4] and European data. [13] Unlike those series, we report prospectively collected data from the setting of an established national breast screening programme, with built in quality assurance of imaging, surgery, pathology and RT. [11, 14] An additional major strength, in contrast to other studies including the randomised clinical trials, is the prospective collection of margin status, an area of significant international controversy. In addition, available data include the use of endocrine therapy with linkage to outcomes. [3, 4] Conversely, one limitation of the present study, in keeping with the recently published retrospective series [3-5, 13] is its observational nature with the consequent difficulty in accounting for all possible confounders. Follow up is also relatively short in the context of the long natural history of DCIS.

Breast conservation was the definitive surgery for 70.5% of women, more frequently used with increasing age. This may reflect perceptions about risk of within breast recurrence in younger patients. Whilst it is likely that RT following BCS was used in patients perceived (based on

pathological and patient-related factors) to be at higher risk of recurrence, RT use was, surprisingly, not associated with close or involved circumferential resection margins. Conversely, mastectomy was, not unexpectedly, associated with features of more aggressive DCIS.

RT following BCS was associated with a significant reduction in all ipsilateral breast further events (DCIS or invasive) at a median follow up of 64 months. The association of RT with reduced recurrence risk is consistent with the effects seen in the overview of the prospective randomized trials. [15] Significantly, however, in the present study, the reduction of breast recurrence associated with RT was independent of margin of excision. Differing minimum margin widths for DCIS have been proposed [16, 17]. One recent series has suggested that a 1mm margin may be sufficient, with or without RT [18]. Others have suggested that those with margin widths <1mm may benefit from postoperative radiation therapy whilst those with >10mm margins receive no benefit with regard to recurrence. [19] However, specifically for women who did not receive RT, in this series there was an association between a DCIS margin of <2mm and ipsilateral breast recurrence. This provides direct evidence in support of more recent reviews, meta-analysis and consensus guidelines [20, 21] as well as recent studies [22].

The higher all-cause mortality in patients not receiving RT after BCS is likely to reflect comorbidities not captured in the current study. Nevertheless, patients not receiving RT had a higher (7.2%) breast recurrence rate, confirming patient selection for RT could be improved. [23]

Endocrine therapy was associated with a non-significant reduction in ipsilateral breast recurrence independent of RT, although the greatest effect was seen for the reduction of invasive further events in the absence of RT. In a contemporary analysis of the US retrospective National Cancer Data Base (70% of the US population), 36.5% of women (most commonly between 50 and 59 years of age) received adjuvant endocrine therapy for DCIS [24] compared with 12.2% in this UK-based study, and no-one in a cohort in the Netherlands [13], reflecting the inconsistent interpretation of evidence from trials examining the impact of endocrine therapy for DCIS on local recurrence, the associated toxicities and issues of adherence to adjuvant tamoxifen treatment.

Significantly, neither the use of RT, endocrine therapy, nor type of surgery, appeared to influence breast cancer mortality, although women who developed invasive ipsilateral breast cancer had a poorer survival than those who had DCIS recurrence. Indeed, breast cancer mortality (0.46%) was a fifth of other cause mortality, in keeping with several retrospective studies. [3, 4, 13]

The increasing incidence of DCIS, likely to be sustained with the enhanced visualisation that digital mammography provides, now deployed in the UK NHS BSP, emphasises the potential for overtreatment of women diagnosed through breast screening. [1,25] Since digital mammography was not deployed during the time of data collection for this study, the impact of digital mammography and any influences on the data reported here remain uncertain. However, the present study findings do re-emphasise the issue of potential overtreatment of DCIS and the need to improve the selection of adjuvant therapy for women with DCIS. This requires a greater understanding of the underlying biology of DCIS, on reliable predictive and prognostic assessment, particularly to select women at risk of invasive breast cancer recurrence. Predictive models of ipsilateral breast recurrence after DCIS, and a more recent prognostic score for DCIS for RT benefit, require prospective validation if they are to be widely adopted. [26-30] Meanwhile, a major international initiative between the UK, Netherlands and the US, the PRECISION (PREvent ductal Carcinoma In Situ Invasive Overtreatment Now) study funded by Cancer Research UK and the Dutch Cancer Society seeks to define underlying molecular mechanisms in DCIS related to risk of progression and, together with diagnostic and clinical elements, construct risk models for the future management of patients.

(<http://www.cancerresearchuk.org/funding-for-researchers/how-we-deliver-research/grand-challenge-award/funded-teams-wesseling>) [30] Emulating studies in prostate, thyroid and renal neoplasia, active surveillance, rather than initial surgery, for carefully selected patients with low risk DCIS has been advocated and may avoid the potential sequelae of breast surgery. Indeed, prospective randomised trials of active surveillance versus conventional surgical care, e.g. the LOW RISK DCIS (LORIS) trial in the UK, COMET in the USA and LORD in mainland Europe [31-33] seek to identify a cohort of patients with sufficiently low risk to obviate the need for surgical excision.

Conclusions

This large prospective cohort study allows us to examine, in contemporary practice, the effects of present-day treatments, and the patient and pathological features that have previously been described in retrospective studies and randomised clinical trials. The reduction in recurrence rates seen with the use of RT and endocrine therapy has not, to date, yielded a survival benefit to patients, although other-cause mortality is five times greater than that attributable to breast cancer. Ipsilateral breast recurrence risk is, however, higher in patients treated by BCS without RT, particularly if the radial excision margin is narrow (<2mm). Women with recurrence as invasive disease have poorer survival than those with recurrent DCIS and further research targeting clinical, biological and imaging

biomarkers of risk of invasive recurrence after a diagnosis of screen-detected DCIS is indicated, to improve personalisation of therapy and outcomes.

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* Indicates former members of the steering group

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Appendix

UK Breast Screening Units contributing to the Sloane Project:

Avon	North Derbyshire
Barking, Havering, Redbridge & Brentwood	North East Scotland
Barnsley	North Lancashire & South Cumbria
Bedfordshire & Hertfordshire	North London
Bolton, Bury & Rochdale	North Nottinghamshire
Breast Test Wales – North*	North Staffordshire
Breast Test Wales – South East*	North Yorkshire
Breast Test Wales – South West*	Northampton
Cambridge & Huntingdon	Nottingham
Central & East London	Oxfordshire
Chelmsford & Colchester	Pennine (Bradford)
Chester	Peterborough
City, Sandwell & Walsall	Portsmouth
Cornwall	Rotherham
Crewe	Sheffield

Doncaster	Shropshire
Dorset	Somerset
Dudley & Wolverhampton	South Birmingham
East Berkshire (Windsor)	South Derbyshire
East Cheshire & Stockport	South Devon
East Lancashire	South East London & Queen Mary's
East Scotland	South East Scotland
East Sussex, Brighton & Hove	South Essex
Gateshead	South Staffordshire
Gloucestershire	South West London (St George's)
Great Yarmouth & Waveney	South West Scotland
Greater Manchester	Southampton & Salisbury
Hereford & Worcester	Surrey (Jarvis)
Humberside	Warrington
Isle of Wight	Warwickshire, Solihull & Coventry
King's Lynn	West Berkshire
Leeds & Wakefield	West Devon & East Cornwall
Leicestershire	West Essex
Liverpool	West of London
Maidstone	West of Scotland
Medway (Gillingham, Kent)	West Suffolk
Milton Keynes	Western, Northern Ireland*
Newcastle-Upon-Tyne	Wiltshire
Norfolk & Norwich	Wirral
North & Eastern Devon	Wycombe
North & Mid Hampshire	
North Cumbria	

* Unit data not included in these analyses

Table 1: Radiotherapy (RT) use & pathological features after breast conservation surgery (BCS).

Pathological feature	No RT (% all cases)	RT (% all cases)	All cases (% with each feature type)
Total number of cases	5,497 (55.3)	4,396 (44.2)	9,938 (100.0)
Number of BCS cases	2,616 (37.3)	4,363 (62.3)	7,007 (70.5)
Number of Mx cases	2,881 (98.3)	33 (1.1)	2,931 (29.5)
Cytonuclear grade			
High	770 (19.2)	3,240 (80.6)	4,020 (57.4)
Intermediate	1,223 (54.9)	993 (44.6)	2,227 (31.8)
Low	616 (82.1)	127 (16.9)	750 (10.7)
Unknown	7 (70.0)	3 (30.0)	10 (0.1)
Tumour size (mm)			
<10	1,403 (58.0)	1,002 (41.44)	2,418 (34.5)
10 - <20	808 (33.2)	1,619 (66.5)	2,434 (34.7)
20 - <30	247 (19.4)	1,022 (80.2)	1,274 (18.2)
30 - <40	85 (16.7)	423 (82.9)	510 (7.3)
40 - <50	33 (15.8)	176 (84.2)	209 (3.0)
50+	26 (19.0)	110 (80.3)	137 (2.0)
Unknown	14 (56.0)	11 (44.0)	25 (0.4)
Microinvasion			
Yes	70 (19.0)	298 (81.0)	368 (5.3)
No	2,519 (38.4)	4,020 (61.2)	6,566 (93.7)
Unknown	27 (37.0)	45 (61.6)	73 (1.0)
Comedo necrosis			
Yes	1,006 (24.3)	3,116 (75.3)	4,137 (59.0)
No	1,431 (59.2)	975 (40.4)	2,416 (34.5)
Unknown	179 (39.4)	272 (59.9)	454 (6.5)
Radial margin (mm)			
0	72 (34.6)	132 (63.5)	208 (3.0)
>0 to <1	72 (35.5)	129 (63.6)	203 (2.9)
1 - <2	183 (35.0)	337 (64.4)	523 (7.5)
2 - <5	480 (34.5)	907 (65.2)	1,391 (19.9)
5 - <10	642 (35.2)	1,176 (64.5)	1,823 (26.0)
10+	1,055 (41.4)	1,486 (58.3)	2,547 (36.4)
Unknown	112 (35.9)	196 (62.8)	312 (4.5)

Figure 1: 9938 UK patients with screen-detected DCIS (2003-2012).

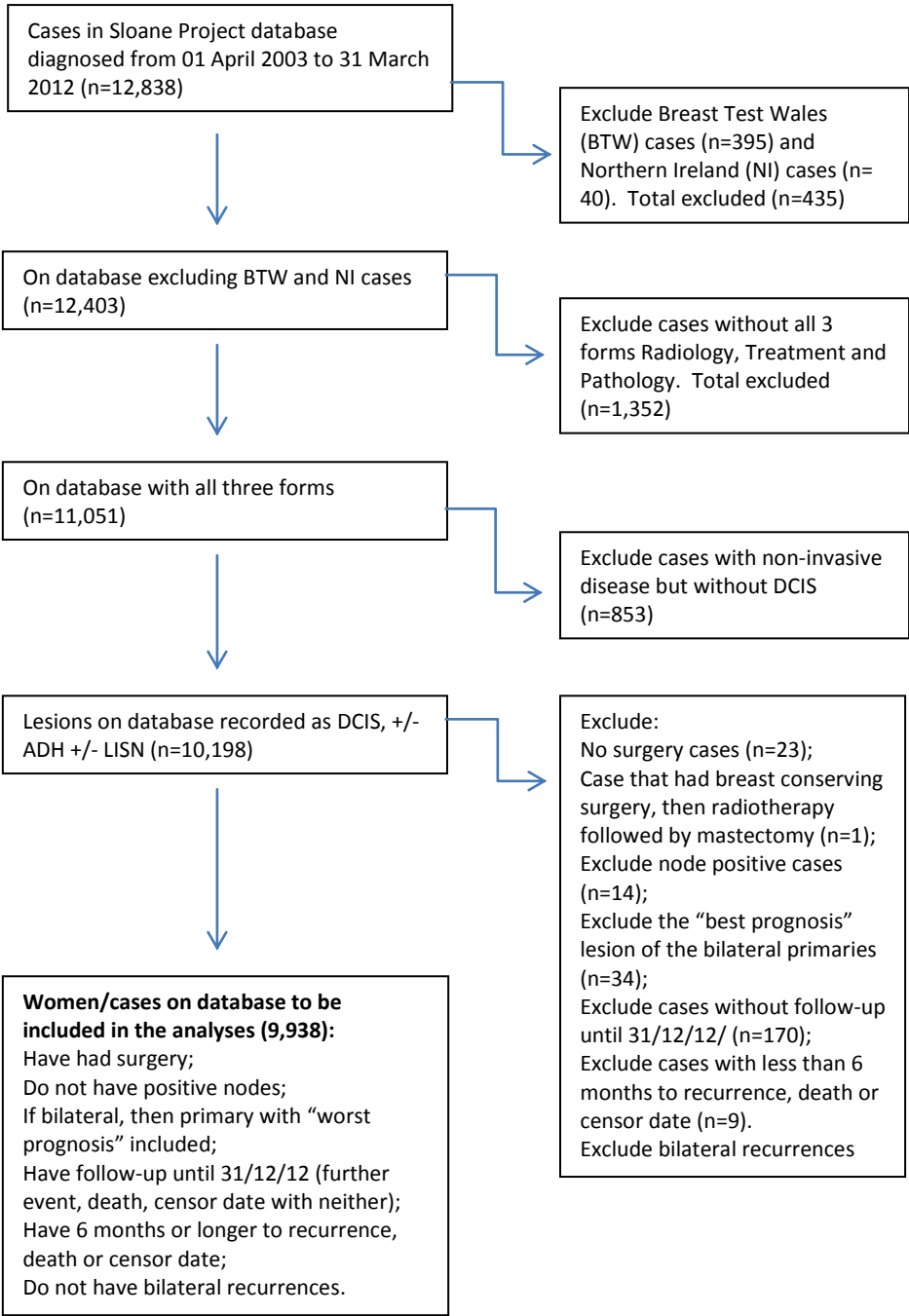
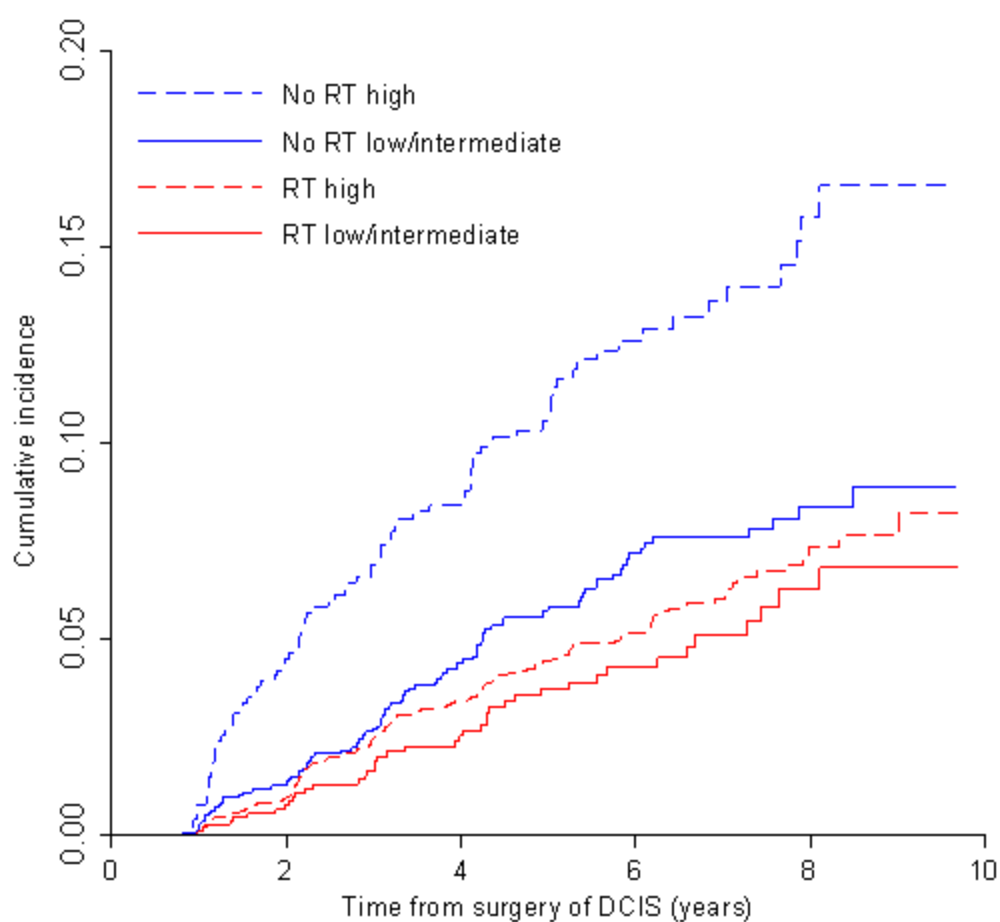
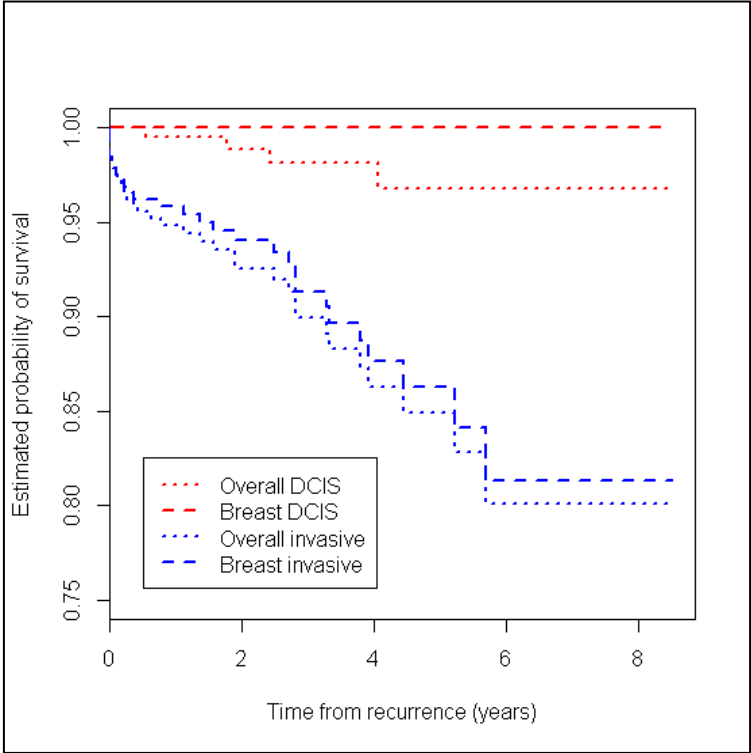


Figure 2: Radiotherapy (RT) and ipsilateral breast events.



	Time from surgery of DCIS				
	0	2	4	6	8
Number at risk					
RT low/int	1120	969	688	441	180
RT high	3240	2763	1898	1098	420
No RT low/int	1839	1587	1138	684	275
No RT high	770	665	492	308	119
Cumulative censoring					
RT low/int	0	133	380	602	850
RT high	0	424	1172	1904	2553
No RT low/int	0	199	569	965	1356
No RT high	0	54	185	336	508

Figure 3: Survival from the date of recurrence



	Time from recurrence				
	0	2	4	6	8
Number at risk					
Overall DCIS	226	149	73	27	3
Overall Invasive	322	179	78	23	2
Breast DCIS	226	149	73	27	3
Breast Invasive	322	179	78	23	2
Cumulative censoring					
Overall DCIS	0	75	150	195	219
Overall Invasive	0	122	215	267	288
Breast DCIS	0	77	153	199	223
Breast Invasive	0	126	219	271	292

Conflict of Interest declaration

See manuscript for details and attached ICMJE forms

Supplementary Text or Table (online publication only)

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